Compounds V and VII were similarly injected daily in doses of 1.4 μmoles, *i.e.*, at 200 times the thyroxine level. The results of the assay, listed in Table II, fail to show any thyromimetic or antithyroid effect of compounds V and VII. Compound VI was found inactive at 1000 times the thyroxine dose in a previous experiment.

Phosphinylguanidines. Phosphorus Analogs of Biguanides

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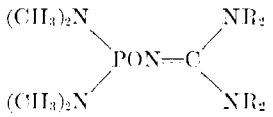
Many biguanides display the ability to lower the blood-sugar levels of animals.[1] In this communication we describe the synthesis of two phosphinylguanidines of type **1**. These compounds represent examples of a



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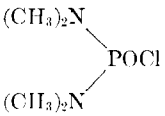

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novel system in which one of the carbon atoms of a biguanide skeleton has been replaced with a P=O unit.

The reactions of commercially available N,N′-bisdimethylphosphorodiamidic chloride (**2**) with guanidine[2] and 1,1,3,3-tetramethylguanidine gave 2-[bis(dimethylamino)phosphinyl]guanidine (**1**, R = H) and 2-[bis(dimethylamino)phosphinyl]-1,1,3,3-tetramethylguanidine (**1**, R = CH_3), respectively. The phosphinylguanidines 1 were administered as suspensions in 0.5% sodium carboxymethylcellulose solution orally at 250 mg/kg to normal chicks and intraperitoneally at 200 mg/kg to normal rats. Blood glucose levels, estimated as "reducing sugar" content by the method of Hoffman as modified for the Technicon Auto-Analyzer,[3] were not depressed significantly below controls when determined at 2 hr after dosing for chicks and 3 hr after dosing for rats.

Experimental Section[4]

2-[Bis(dimethylamino)phosphinyl]guanidine.—To 5.5 g (0.094 mole) of guanidine[2] was added dropwise with stirring and ice-bath cooling during 15 min 8.2 g (0.048 mole) of N,N′-bisdimethylphosphorodiamidic chloride. The mixture was allowed to stand for 16 hr at room temperature, taken up in hot acetonitrile, and filtered. Upon cooling, a solid, 1.6 g, mp 170–180°, separated from the filtrate and was collected. Recrystallization from acetonitrile gave 1.0 g (11%) of colorless needles: mp 179–182° dec; infrared (KBr disk), strong bands at 2.9 (NH), 8.8 (P=O), and 10.1 μ (PN).[5]

Anal. Calcd for $C_5H_{16}N_5OP$: C, 31.09; H, 8.29; N, 36.27. Found: C, 30.35; H, 8.07; N, 36.43.

The compound was converted to the picrate, yellow needles, mp 207–208° (from ethanol).

Anal. Calcd for $C_{11}H_{19}N_8O_8P$: C, 31.28; H, 4.50; N, 26.54; P, 7.35. Found: C, 31.43; H, 4.55; N, 25.99; P, 7.21.

2-[Bis(dimethylamino)phosphinyl]-1,1,3,3-tetramethylguanidine.—With stirring, 12.0 g (0.1 mole) of 1,1,3,3-tetramethylguanidine and 8.5 g (0.05 mole) of N,N′-bisdimethylphosphorodiamidic chloride were mixed. After the exothermic reaction subsided, the mixture was heated on a steam bath for 30 min under nitrogen. The mixture was taken up in ether and filtered, and the filtrate was concentrated under reduced pressure to a liquid containing some solid. After filtration, the material was distilled to give 5.8 g of colorless liquid, bp 130–135° (0.5 mm). Redistillation gave 3.9 g (31%) of colorless liquid: bp 123–126° (0.3 mm); infrared ($CHCl_3$), strong bands at 8.6 (P=O) and 10.1 μ (PN).[5]

Anal. Calcd for $C_9H_{24}N_5OP$: C, 43.37; H, 9.63; N, 28.11; P, 12.44. Found: C, 42.98; H, 9.75; N, 27.21; P, 12.48.

The compound was converted to the picrate, yellow prisms, mp 168–169° (from ethanol).

Anal. Calcd for $C_{15}H_{27}N_8O_8P$: C, 37.66; H, 5.65; N, 23.43; P, 6.49. Found: C, 38.00; H, 5.61; N, 23.37; P, 6.73.

(1) Salts of phenethylbiguanide, 1,1-dimethylbiguanide, and *n*-butylbiguanide are utilized in the clinical control of diabetes: L. J. P. Duncan and B. F. Clarke, *Ann. Rev. Pharmacol.*, **5**, 151 (1965).

(2) W. Marckwald and F. Struwe, *Ber.*, **55**, 458 (1922).

(3) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937). The animal testing was carried out by Drs. C. Boshart, S. Gordon, and E. Tocus of these laboratories.

(4) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff.

(5) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p 405.

Salts of α-Amino-*p*-toluenesulfonamide

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α-Amino-*p*-toluenesulfonamide[1] has been in the armamentarium of the physician as a broad-spectrum antibacterial agent for almost a quarter century. It was synthesized and described by Klarer[2,3] and its outstanding therapeutic properties were first reported by Domagk[4] and summarized by Northey.[5]

Recently, it was found that this sulfonamide hydrochloride was a useful topical agent in burn wound sepsis.[6,7] However, some patients, particularly those who were treated with large quantities of this drug, developed metabolic acidosis. In order to overcome this side effect we have prepared a series of new organic salts (Table I).

The chemical isolation of the acetate, the salt of choice, now undergoing clinical trials, has not been reported in the literature, and it was only alluded to as a potentially useful compound.[8,9] Its use for the treatment of burns, in a hydrophillic ointment base, has successfully overcome the problem of metabolic acidosis.

Skulan and Hoppe[10] infused 0.5 *M* aqueous solutions of the hydrochloride and acetate salts in the marginal ear veins of unanesthetized nonfasted male rabbits. The hydrochloride produced a marked progressive fall in blood pH and plasma total CO_2 concentration,

(1) Also known as α-aminomethylbenzenesulfonamide, homosulfanilamide, Sulfamylon®, marfanil, mafenide, etc.

(2) J. Klarer, *Klin. Wochschr.*, **20**, 1250 (1941).

(3) J. Klarer, U. S. Patent 2,288,531 (1942).

(4) G. Domagk, *Klin. Wochschr.*, **21**, 448 (1942).

(5) E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948, p 252.

(6) R. B. Lindberg, R. E. Brame, J. A. Moncrief, and A. D. Mason, *Federation Proc.*, **23**, 1725 (1964).

(7) R. B. Lindberg, J. A. Moncrief, W. E. Switzer, S. E. Order, and W. Miller, *J. Trauma*, **5**, 601 (1965).

(8) J. A. Mendelson and F. B. Brinkley, U. S. Patent 3,230,140 (1966).

(9) J. A. Moncrief, R. B. Lindberg, W. E. Switzer, and B. A. Pruitt, Jr., *Arch. Surg.*, **92**, 558 (1966).

(10) T. W. Skulan and J. O. Hoppe, *Life Sci.*, in press.